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**TRANSMITTAL LETTER TO THE UNITED STATES  
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INTERNATIONAL APPLICATION NO.

PCT/FR00/02282

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TITLE OF INVENTION: MICROPARTICLES FOR PULMONARY ADMINISTRATION

APPLICANTS FOR DO/EO/US: 1) Joël RICHARD, 2) Claire DULIEU, 3) Dominique LE MEURLAY, and  
4) Jean-Pierre BENOIT

Applicants herewith submit to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c)(2)).
  - a. ☒ is attached hereto (required only if not communicated by the International Bureau).
  - b. ☐ has been communicated by the International Bureau.
  - c. ☐ is not required, as the application was filed with the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371 (c)(2)).
  - a. ☒ is attached hereto.
  - b. ☐ has been previously submitted under 35 U.S.C. 154 (d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3)).
  - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
  - b. ☐ have been communicated by the International Bureau.
  - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
  - d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☐ Information Disclosure Statement under 37 CFR 1.97 and 1.98
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A Substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821-1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154 (d)(4).
19. ☐ A second copy of the English language translation of the international application 35 U.S.C. 154 (d)(4).
20. ☒ Other items or information:
  - a. ☒ Copy of cover page of International Publication No. WO 01/12160 A1.
  - b. ☐ Copy of Notification of Missing Requirements.
  - c. ☒ Declaration of the translator (verification of translator)

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a. ☒ A check in the amount of \$ 1210.00 to cover the above fees is enclosed.

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Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.  
1300 I Street, N.W.  
Washington, D.C. 20005-3315  
EFC/FPD/sci  
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SIGNATURE

Ernest F. Chapman/25,961

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VERIFICATION OF A TRANSLATION

I, the below named translator, hereby declare that:

My name and post office address are as stated below;

That I am knowledgeable in the French language in which the below identified international application was filed, and that, to the best of my knowledge and belief, the English translation of the international application No. PCT/FR00/02282 is a true and complete translation of the above identified international application as filed.

I hereby declare that all the statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the patent application issued thereon.

Date: January 25, 2002



Full name of the translator :

Elaine Patricia PARRISH

For and on behalf of RWS Group plc

Post Office Address :

Europa House, Marsham Way,  
Gerrards Cross, Buckinghamshire,  
England.

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**"Microparticles for pulmonary administration"**

5 The present invention relates to the domain of micro-  
 particles intended to be administered via the pulmonary  
 route.

10 A bibliographical study has made it possible to  
 demonstrate that a great deal of research relating to  
 this technology has been carried out.

15 Aerosols for releasing therapeutic agents into the  
 respiratory tracts have been described for example  
 (Adjei, A and Garren, J. Pharm. Res., 7: 565-569  
 (1990); and Zanen, P. and Lamm, J.W.J. Int. J. Pharm.,  
 114: 111-115 (1995)). The respiratory tracts comprise  
 the upper respiratory tracts, which include the larynx  
 and the oropharynx, and the lower respiratory tracts,  
 which include the trachea which extends into  
 bifurcations: the bronchi and the bronchioles. The  
 20 terminal bronchioles then divide into respiratory  
 bronchioles which lead to the ultimate zone of the  
 respiratory system, the pulmonary alveoli, also named  
 the deep lung (Gonda, I. "Aerosols for delivery of  
 therapeutic and diagnostic agents in the respiratory  
 25 tract", in Critical Reviews in Therapeutic Drug Carrier  
 Systems, 6: 273-313 (1990)). The deep lung, or the  
 alveoli, is (are) the main target for therapeutic  
 aerosols, by inhalation, intended for the systemic  
 pathway. Aerosols intended to be inhaled have already  
 30 been used for the treatment of local pulmonary  
 disorders, such as asthma and cystic fibrosis (Anderson  
 et al., Am. Rev. Respir. Dis., 140: 1317-1324 (1989)).  
 In addition, they can be used for the systemic release  
 of peptides and of proteins (Patton and Platz, Advanced  
 35 Drug Delivery Reviews, 8: 179-196 (1992)). However, a  
 certain number of difficulties are encountered when the  
 intention is to apply the release of medicinal products

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by the pulmonary route to the release of macro-  
molecules. Among these difficulties, there is the  
denaturation of the protein during nebulization, a  
significant loss of the amount of medicinal products  
5 inhaled in the oropharynx (which often exceeds 80%),  
poor control of the area of deposition, poor  
reproducibility of the therapeutic results due to the  
variations in respiratory models, too rapid an  
absorption of the medicinal products, generating local  
10 toxic effects, and phagocytosis by the macrophages of  
the lung.

The human lung can rapidly eliminate or degrade  
hydrolyzable products deposited in the form of  
15 aerosols, this phenomenon generally occurring over a  
period of between a few minutes and a few hours. In the  
upper pulmonary tracts, the ciliated epithelium  
contributes to the "mucociliary escalator" phenomenon  
by which particles are led from the pulmonary tracts to  
20 the mouth (Pavia, D. "Lung Mucociliary Clearance, "in  
"Aerosols and the Lung: Clinical and Experimental  
Aspects, Clarke, S.W. and Pavia, D., Eds.,  
Butterworths, London, 1984.; Anderson et al., Am. Rev.  
Respir. Dis., 140: 1317-1324 (1989)). In the deep lung,  
25 the alveolar macrophages are capable of phagocytosing  
particles immediately after they have been deposited.

Local and systemic therapies by inhalation generally  
allow controlled and relatively slow release of the  
30 active principle (Gonda, I., "Physico-chemical  
principles in aerosol delivery", in: Topics in  
Pharmaceutical Sciences 1991, D.J.A. Crommelin and K.K.  
Midha, Eds., Stuttgart: Medpharm Scientific Publishers,  
pp. 95-117 (1992)). The slow release of the therapeutic  
35 aerosol may prolong the period of time for which the  
medicinal product administered remains in the pulmonary  
tracts or in the acini, and decrease the rate of entry  
of the medicinal products into the blood stream. Thus,

the patient's tolerance is increased by reducing the frequency of the administrations (Langer, R., Science, 249: 1527-1533 (1990); and Gonda, I. "Aerosols for delivery of therapeutic and diagnostic agents to the respiratory tract", in Critical Reviews in Therapeutic Drug Carrier Systems 6: 273-313 (1990)).

Among the drawbacks represented by dry powder formulations, there is the fact that powders of ultrafine particles have flow and nebulization properties which are generally poor, leading to the production of aerosol fractions which are admitted into the respiratory system relatively slowly, these fractions of the inhaled aerosol generally being deposited in the mouth and in the throat (Gonda, I., in Topics in Pharmaceutical Sciences 1991, D. Crommelin and K. Midha, Editors, Stuttgart: Medpharm Scientific Publishers, 95-117 (1992)).

The main problem encountered with most aerosols is the particulate aggregation generated by the interparticle interactions, such as the hydrophobic, electrostatic and capillary interactions. An effective therapy by inhalation of dry powder for both the immediate and sustained release of therapeutic agents, both locally and systemically, requires the use of a powder having minimal aggregation which makes it possible to avoid or at least to suspend the mechanisms of natural clearance of the lung until the moment when the active principle is released.

There is currently a need for improved inhalation aerosols intended for the pulmonary release of therapeutic agents. Similarly, there is currently a need for medicinal product supports which are capable of releasing the medicinal product in an effective amount in the pulmonary tracts or in the alveolar regions of the lungs.

In addition there is also a need for medicinal product supports which may be used as inhalation aerosols which are biodegradable and which make it possible to release the medicinal products in a controlled manner in the respiratory tracts and the alveolar region of the lungs, and similarly, there is a need for particles for the release of medicinal product in the lungs, which have improved nebulization properties. These investigations tend to show that it is difficult to prepare microparticles which correspond to the criteria imposed on them by them being used under effective conditions.

In order to exhibit sufficient effectiveness, these microparticles must not be damaged during administration, when they pass into nebulized form. The bioavailability of these microparticles must reach a sufficiently high value; however, the bioavailability of the microparticles of the prior art does not generally exceed 50%, due to a low level of deposition of the microparticles in the alveolar pulmonary regions.

In addition, in order to conserve their effectiveness during pulmonary administration, the microparticles, once deposited in the alveoli, must be sufficiently stable in the mucus of the surface of these alveoli.

Thus, it may prove interesting to prepare microparticles for immediate or delayed release, locally or systemically; however, these microparticles generally have an external layer the thickness of which relative to the diameter of said particle is not insignificant.

The microparticles according to the invention consist of a core containing the active material coated with a layer of coating agent deposited by the supercritical fluid technique. This particular structure

distinguishes them from the microparticles of the prior art, which are matricial microspheres obtained using techniques of emulsifying-evaporating solvent, of extracting solvent with aqueous phases or of  
5 nebulization-drying organic solvent.

Consequently, the present invention relates to biocompatible microparticles intended to be inhaled, comprising at least one active principle and at least  
10 one layer coating this active principle, which is the external layer of said microparticles, said external layer containing at least one coating agent, said microparticles having a mean diameter of between 1  $\mu\text{m}$  and 30  $\mu\text{m}$  and an apparent density of between 0.2  $\text{g}/\text{cm}^3$   
15 and 0.8  $\text{g}/\text{cm}^3$ , and it being possible to obtain them according to a method comprising the essential steps which are bringing together a coating agent and an active principle and introducing a supercritical fluid, with stirring in a closed reactor.

20 These microparticles do not aggregate when they are administered and may, optionally, allow sustained release of the active principle. The microparticles according to the invention exhibit a bioavailability of  
25 greater than 60%, and preferably greater than 80%, due to an improvement in the level of deposition of the particles in the alveolar pulmonary regions.

It has thus been demonstrated that the implementation  
30 of a method for preparing microparticles using a "supercritical fluid" technique using, as a coating agent, judiciously chosen biocompatible materials makes it possible to obtain microparticles of controlled size and which have a surface finish such that said  
35 microparticles do not aggregate and deposit in the alveolar pulmonary regions.

The biocompatible microparticles intended for

inhalation according to the invention have an external layer comprising a coating agent which prevents these particles aggregating with one another. The degree of covering of the surface area of the particles is at least greater than 50%, preferably greater than 70%, even more preferentially greater than 85%. The quality of this coating is essentially due to the supercritical fluid technique.

- 10 Said method comprises two essential steps which are bringing together a coating agent and an active principle and introducing a supercritical fluid in order to ensure the coacervation of the coating agent. It clearly emerges from the remainder of the description that these two steps do not have to be carried out in the order stated.

The first method for preparing the microparticles according to the invention differs from the second method by the fact that the coating agent is at no moment in solution in the fluid in the liquid or supercritical state.

Specifically, a first implementation of the method according to the invention comprises the following steps:

- suspending an active principle in a solution of at least one substantially polar coating agent in an organic solvent,
- 30 said active principle being insoluble in the organic solvent,
- said substantially polar coating agent being insoluble in a fluid in the supercritical state,
- said organic solvent being soluble in a fluid in the supercritical state,
- 35 - bringing the suspension into contact with a fluid in the supercritical state, so as to desolvate in a controlled way the substantially polar coating

- agent and ensure its coacervation,
- substantially extracting the solvent using a fluid in the supercritical state and discharging the supercritical fluid/solvent mixture,
  - 5 - recovering the microparticles.

The fluid used for the implementation of this first method is preferably liquid CO<sub>2</sub> or CO<sub>2</sub> in the supercritical state.

10

The organic solvent used for the implementation of this first method is generally chosen from the group consisting of ketones, alcohols and esters.

- 15 The supercritical fluid is brought into contact with the suspension of active principle containing the coating agent in solution by introducing the supercritical fluid into an autoclave which already contains the suspension.

20

When the supercritical fluid used is CO<sub>2</sub>, it is possible to use CO<sub>2</sub> in the liquid form or to directly use CO<sub>2</sub> in the supercritical state.

- 25 According to another variant, it is also possible to bring the suspension into contact with liquid CO<sub>2</sub> which will then go into the supercritical state by increasing the pressure and/or the temperature in the autoclave in order to extract the solvent.

30

When use of the liquid CO<sub>2</sub> variant is chosen, the temperature is preferably chosen between 20 and 30°C and the pressure between 80 and 150 10<sup>5</sup> Pa. When the supercritical CO<sub>2</sub> variant is used, the temperature is  
35 generally chosen between 35 and 60°C, preferably between 35 and 50°C, and the pressure between 80 and 250 10<sup>5</sup> Pa, preferably between 100 and 220 10<sup>5</sup> Pa.

The mass of organic solvent introduced into the autoclave represents at least 3%, preferably between 3.5% and 25%, of the mass of the supercritical fluid or liquid used to cause the dissolvation of the coating agent. The microparticles obtained by implementing this first method have an external layer virtually free of solvent; the amount of solvent in the external layer is, in fact, less than 500 ppm.

10 The coating agents which can be used for the implementation of this first method are more particularly:

- biodegradable (co)polymers of  $\alpha$ -hydroxycarboxylic acids, in particular homopolymers and copolymers of lactic acid and glycolic acid, and more particularly PLAs (poly-L-lactide) and PLGAs (poly(lactic-co-glycolic acid)),
- amphiphilic block polymers of the poly(lactic acid)-poly(ethylene oxide) type,
- 20 - biocompatible polymers of the poly(ethylene glycol), poly(ethylene oxide) type,
- polyanhydrides, poly(ortho esters), poly- $\epsilon$ -caprolactones and derivatives thereof,
- poly( $\beta$ -hydroxybutyrate), poly(hydroxyvalerate) and poly( $\beta$ -hydroxybutyrate-hydroxyvalerate) copolymers,
- 25 - poly(malic acid),
- polyphosphazenes,
- block copolymers of the poly(ethylene oxide)-poly(propylene oxide) type,
- 30 - poly(amino acids),
- polysaccharides,
- phospholipids such as phosphatidyl glycerols, diphosphatidyl glycerols containing C12 to C18 fatty acid chains (DLPG, DMPG, DPPG, DSPG), phosphatidylcholines, diphosphatidylcholines containing C12 to C18 fatty acid chains (DLPC, DMPC, DPPC, DSPC), diphosphatidylethanolamines
- 35

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- 5 containing C12 to C18 fatty acid chains (DLPE, DMPE, DPPE, DSPE), diphosphatidylserine containing C12 to C18 chains (DLPS, DMPS, DPPS, DSPS), and mixtures which contain the phospholipids mentioned,
- 10 - fatty acid esters such as glyceryl stearates, glyceryl laurate, cetyl palmitate, or mixtures which contain these compounds,
- mixtures which contain the abovementioned compounds.

15 The implementation of the second method according to the invention consists in suspending an active principle in a supercritical fluid containing at least one coating agent dissolved therein, and then in modifying the conditions of pressure and/or of temperature of the environment so as to ensure the coacervation of the particles, by precipitation of the coating agent around the particles of active principle,

20 i.e. to ensure the coacervation of the particles by physicochemical modification of the environment.

25 The coating agents which can be used for the implementation of this second method are more particularly:

- 30 - phospholipids such as phosphatidyl glycerols, diphosphatidyl glycerols containing C12 to C18 fatty acid chains (DLPG, DMPG, DPPG, DSPG), phosphatidylcholines, diphosphatidylcholines containing C12 to C18 fatty acid chains (DLPC, DMPC, DPPC, DSPC), diphosphatidylethanolamines containing C12 to C18 fatty acid chains (DLPE, DMPE, DPPE, DSPE), diphosphatidylserine containing C12 to C18 chains (DLPS, DMPS, DPPS, DSPS), and
- 35 mixtures which contain the phospholipids mentioned,
- mono-, di-, triglycerides in which the fatty acid chains range from C4 to C22, and mixtures

- containing them,
- mixtures of glycerides and of esters of polyethylene glycol,
  - cholesterol,
  - 5 - fatty acid esters such as glyceryl stearates, glyceryl laurate or cetyl palmitate,
  - mixtures which contain the abovementioned compounds.
- 10 The biodegradable or bioerodible polymers soluble in a supercritical fluid may also be used in this second method.
- The coacervation (or aggregation) of a coating agent is
- 15 caused by physicochemical modification of an environment containing an active substance in suspension in a solution of a coating agent in a solvent, said solvent being a supercritical fluid.
- 20 The supercritical fluid preferentially used is supercritical  $\text{CO}_2$  ( $\text{SCCO}_2$ ), the typical initial functioning conditions of this second method will be approximately 31 to 80°C and the pressures will be 75 to 250  $10^5$  Pa, although higher values may be used for
- 25 one or other of the two parameters, or both, on condition, of course, that the higher values have no harmful or degradation effect on the active principle being covered, or on the coating agents.
- 30 Moreover, it is also possible to choose other fluids commonly used as supercritical fluids. Mention will be made in particular of ethane, which becomes supercritical above 32°C and 48  $10^5$  Pa, nitrogen dioxide, the critical point of which is 36°C and 72  $10^5$
- 35 Pa, propane, the critical point of which is 96°C and 42  $10^5$  Pa, trifluoromethane, the critical point of which is 26°C and 47  $10^5$  Pa, and chlorotrifluoromethane, the critical point of which is 29°C and 39  $10^5$  Pa.

This second method involves suspending, in a closed stirred autoclave, an active principle which is insoluble in the supercritical fluid, said  
5 supercritical fluid containing a coating agent which is in the state of a solute.

The pressure and/or the temperature are then modified so as to decrease the solubility of the coating agent  
10 in the fluid. Thus, the affinity of the coating agent for the active principle increases such that this coating adsorbs around the active principle. Once this coating agent is deposited over the active principle, the autoclave is depressurized and the microparticles  
15 are recovered.

To implement this second method, the active principle to be covered and the coating agent(s) are placed in an autoclave equipped with a stirrer, and then the system  
20 is pressurized by introducing into the autoclave a fluid presented under supercritical conditions. The temperature and/or the pressure inside the autoclave is then modified in a controlled and regulated way so as to gradually decrease the solubility of the coating  
25 agent(s). When the solubility of this or these coating agent(s) in the supercritical fluid decreases, it (they) precipitate(s) and the affinity of these agents for the surface of the active principle leads to them being adsorbed onto this surface. A variant of this  
30 method consists in placing the coating agent in the autoclave before introducing the active principle therein or while simultaneously introducing therein the active principle and a fluid capable of passing into the supercritical state. The pressurization of the  
35 autoclave to produce a supercritical fluid state will then cause the coating agent to dissolve in said supercritical fluid.

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According to another variant of the method, the active principle is placed in an autoclave equipped with a stirrer, and the coating agent is placed in a second autoclave equipped with a stirrer, into which the fluid  
5 capable of passing into the supercritical state is introduced. The coating agent is brought to the state of a solute by increasing the temperature and the pressure, and is then transferred into the autoclave which contains the active principle.

10

The coating agent is thus deposited such that this agent covers the surface of the active principle.

The active principle may be in the form of a liquid,  
15 which may thus form an emulsion in the supercritical fluid, of preformed solid particles, and in particular of microparticles optionally already coated, for example, with mono- or disaccharides. The stirring speeds may range between 150 and 700 rpm for the solid  
20 particles and between 600 and 1 000 rpm when the active principle is a liquid.

Such stirring ensures that the active principle is suspended in the supercritical fluid when the latter is  
25 introduced. The supercritical conditions are produced by modifying the temperature and/or the pressure inside the autoclave. Thus, when the supercritical fluid is CO<sub>2</sub>, the temperature of the autoclave is between 35 and 80°C, preferably between 35 and 50°C, and the pressure  
30 is between 100 and 250 10<sup>5</sup> Pa, and preferably between 180 and 220 10<sup>5</sup> Pa.

When the supercritical fluid is ethane, the temperature of the autoclave is between 35 and 80°C, preferably  
35 between 35 and 50°C, and the pressure is between 50 and 200 10<sup>5</sup> Pa, and preferably between 50 and 150 10<sup>5</sup> Pa.

When the fluid is propane, the temperature of the

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autoclave is between 45 and 80°C, preferably between 55 and 65°C, and the pressure is between 40 and 150 10<sup>5</sup> Pa.

- 5 The coating agent is introduced into the autoclave at the same time as the supercritical fluid or before the supercritical fluid is introduced into the autoclave. In any event, in order to ensure good solubilization of the coating agent in the supercritical fluid, the
- 10 system is maintained at equilibrium with stirring, the suitable concentration of active principle and of coating agent is established as a function of the desired microparticles and this equilibrium is left for one hour with stirring. The temperature and the
- 15 pressure are then modulated at a rate sufficiently slow to completely transfer the coating agent(s) from the supercritical fluid to the surface of the active principle, and the system is depressurized in order to isolate the microparticles, which are removed from the
- 20 autoclave.

The microparticles according to the present invention have a diameter of between 1 µm and 30 µm, preferably of between 1 µm and 15 µm, and even more preferably of

25 between 2 µm and 10 µm, and an apparent density of between 0.02 g/cm<sup>3</sup> and 0.8 g/cm<sup>3</sup>, and preferably of between 0.05 g/cm<sup>3</sup> and 0.4 g/cm<sup>3</sup>.

The active principle/coating agent mass ratio of these

30 microparticles is preferably between 95/5 and 5/95.

In the case of controlled-release microparticles, the amount of active principle is small compared to the coating agent, and the active principle/coating agent

35 mass ratio is then between 5/95 and 20/80; on the other hand, when the coating is intended to stabilize the particle, in particular when the microparticle is an immediate-release microparticle, the active principle/-

coating agent mass ratio is generally between 95/5 and 70/30, and preferably between 95/5 and 80/20.

The coating agents of the microparticles according to the invention advantageously belong to the following families:

- biodegradable (co)polymers of  $\alpha$ -hydroxycarboxylic acids, in particular homopolymers and copolymers of lactic acid and glycolic acid, and more particularly PLAs (poly-L-lactide) and PLGAs (poly(lactic-co-glycolic acid)),
- mono-, di-, triglycerides in which the fatty acid chains range from C4 to C22, and mixtures containing them,
- mixtures of glycerides and of esters of polyethylene glycol,
- cholesterol,
- amphiphilic block polymers of the poly(lactic acid)-poly(ethylene oxide) type,
- biocompatible polymers of the poly(ethylene glycol), poly(ethylene oxide) type,
- polyanhydrides, poly(ortho esters), poly- $\epsilon$ -caprolactones and derivatives thereof,
- poly( $\beta$ -hydroxybutyrate), poly(hydroxyvalerate) and poly( $\beta$ -hydroxybutyrate-hydroxyvalerate) copolymers,
- poly(malic acid),
- polyphosphazenes,
- block copolymers of the poly(ethylene oxide)-poly(propylene oxide) type,
- poly(amino acids),
- polysaccharides,
- phospholipids such as phosphatidyl glycerols, diphosphatidyl glycerols containing C12 to C18 fatty acid chains (DLPG, DMPG, DPPG, DSPG), phosphatidylcholines, diphosphatidylcholines containing C12 to C18 fatty acid chains (DLPC, DMPC, DPPC, DSPC), disphosphatidylethanolamines

containing C12 to C18 fatty acid chains (DLPE, DMPE, DPPE, DSPE), diphosphatidylserines containing C12 to C18 chains (DLPS, DMPS, DPPS, DSPS), and mixtures which contain the phospholipids mentioned,

5

- fatty acid esters such as glyceryl stearates, glyceryl laurate or cetyl palmitate,
- mixtures of at least two compounds chosen from the abovementioned fatty derivatives and such that

10 they have suitable solubility.

Depending on the coating agent, the solubility in the supercritical fluids and the coating conditions, the first or the second method described above may thus be

15 implemented.

Said active principle may be in the form of a liquid, of a solid powder or of an inert porous solid particle comprising, on its surface, an active principle.

20

The active principles used are chosen from very varied therapeutic and prophylactic compounds. They are more particularly chosen from proteins and peptides, such as insulin, calcitonin, or analogues of the hormone LH-RH, polysaccharides such as heparin, anti-asthmatic agents, such as budesonide, beclometasone dipropionate and its active metabolite beclometasone 17-monopropionate, beta-estradiol hormones, testosterone, bronchodilators such as albuterol, cytotoxic agents, corticoids,

25

30 antigens and DNA fragments.

Figure 1 is an electron micrograph of a microparticle obtained according to example 2.

35 Figure 2 is an electron micrograph of microparticles obtained according to example 3.

The examples which follow illustrate the invention

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without limiting the scope thereof.

**Example 1**

5 This example illustrates the first method of implementation of the invention.

80 mg of PLGA are solubilized in 80 ml of ethyl acetate. 400 mg of micronized insulin are suspended in  
10 the solution thus obtained at 250 rpm and the suspension is placed in an autoclave with a capacity of 1.0 l. Initially, the pressure is increased to  $100 \cdot 10^5$  Pa by introducing the liquid  $\text{CO}_2$ , while at the same time remaining at a constant temperature of  $28^\circ\text{C}$ .

15 The  $\text{CO}_2$  in the liquid state mixes with the suspension, thus making it possible to wet the insulin and also making it possible to produce the gradual precipitation of the coating agent.

20 The  $\text{CO}_2$  is taken to the supercritical state by gradually increasing the pressure to  $150 \cdot 10^5$  Pa. The temperature is jointly maintained at  $40^\circ\text{C}$ . Thus, the ethyl acetate is extracted. These conditions are  
25 maintained for 15 minutes and then the  $\text{CO}_2$ /ethyl acetate mixture is discharged, by decompressing to  $75 \cdot 10^5$  Pa, in a separator, while maintaining the temperature at a value greater than  $35^\circ\text{C}$ . The ethyl acetate is recovered in this separator and the  $\text{CO}_2$   
30 returns to a reservoir.

The ethyl acetate is recovered and the successive cycles of introducing the liquid  $\text{CO}_2$ , taking it to the supercritical state and discharging the  $\text{CO}_2$  + ethyl  
35 acetate are repeated until the ethyl acetate is completely eliminated.

The decompression necessarily takes place via the

gaseous phase so as not to reconcentrate any coating agent in the remaining ethyl acetate. After the decompression phase, the operation may be repeated several times by reintroducing CO<sub>2</sub> in order to return  
5 to a pressure of  $150 \cdot 10^5$  Pa and a temperature of 40°C. Finally, after depressurization and extraction of the CO<sub>2</sub> + solvent mixture, fresh CO<sub>2</sub> is reintroduced, and is taken to the supercritical state in order to completely extract the solvent. The temperature in this case is  
10 generally between 35 and 45°C and the pressure between 180 and  $220 \cdot 10^5$  Pa.

250 mg of nonaggregated microparticles are thus obtained, which have a mean size of 3 µm, comprising 80  
15 to 90% by weight of insulin and have improved nebulization properties.

#### Example 2

20 This example illustrates the second method of implementation of the invention.

150 mg of bovine serum albumin (BSA) prepared by spray-drying and 600 mg of Gelucire® 50/02 in the form of  
25 chips are placed in a pressurizable and stirred 0.3 l autoclave equipped with a porous insert.

CO<sub>2</sub> is introduced into the autoclave until a pressure of  $95 \cdot 10^5$  Pa is obtained for a temperature of 25°C. The  
30 CO<sub>2</sub> is then in the liquid state.

The stirring is begun and set at 460 rpm. The autoclave is then heated to 50°C. The pressure is then  $220 \cdot 10^5$  Pa; the CO<sub>2</sub> is in the supercritical state and  
35 has a density of 0.805 g/cm<sup>3</sup>.

The system is left to equilibrate for one hour. The temperature of the autoclave is then decreased to 19°C

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over a period of 38 minutes starting from 50°C. The phase in suspension in the supercritical CO<sub>2</sub> thus transforms into a mixture of liquid and gaseous CO<sub>2</sub>, the particles of active principle being in suspension  
5 in the liquid CO<sub>2</sub>. By then depressurizing to atmospheric pressure microparticles of BSA covered with Gelucire® 50/02 are obtained.

250 mg of nonaggregated particles of BSA, with a mean  
10 diameter equal to 10 µm, coated with a layer of Gelucire® 50/02, are thus obtained, the active principle/coating agent mass ratio of which is approximately 30/70. These microparticles have improved nebulization properties.

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### Example 3

This example illustrates the second method of implementation of the invention.

20

300 mg of ovalbumin (OVA) prepared by spray-drying and 300 mg of Gelucire® 50/13 in the form of chips are placed in a pressurizable and stirred 1 l autoclave.

25 CO<sub>2</sub> is introduced into the autoclave until a pressure of  $109 \cdot 10^5$  Pa is obtained for a temperature of 23°C. The CO<sub>2</sub> is then in the liquid state.

The stirring is begun and set at 340 rpm. The autoclave  
30 is then heated to 35°C. The pressure is then  $180 \cdot 10^5$  Pa and the CO<sub>2</sub> is in the supercritical state.

The system is left to equilibrate for one hour. The temperature of the autoclave is then decreased to 16°C  
35 over a period of 43 minutes starting from 35°C. The phase in suspension in the supercritical CO<sub>2</sub> thus transforms into a mixture of liquid and gaseous CO<sub>2</sub>. By then depressurizing to atmospheric pressure

microparticles of OVA covered with Gelucire® 50/13 are obtained.

300 mg of nonaggregated particles of OVA, with a mean diameter equal to 9  $\mu\text{m}$ , coated with a layer of Gelucire® 50/13, are thus obtained, which have improved nebulization properties.

#### Example 4

10

This example illustrates the second method of implementation of the invention.

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300 mg of beclomethasone dipropionate in the form of free powder prepared by spray-drying and 50 mg of dilauroyl phosphatidyl glycerol (DLPG) are placed in a pressurizable 0.3 l autoclave equipped with a porous insert.

20

CO<sub>2</sub> is introduced into the autoclave until a pressure of  $98 \cdot 10^5$  Pa is obtained for a temperature of 23°C. The CO<sub>2</sub> is then in the liquid state.

25

The stirring is begun, at 460 rpm. The autoclave is then heated to 60°C. The pressure is then  $300 \cdot 10^5$  Pa, and the CO<sub>2</sub> is in the supercritical state and has a density of 0.830 g/cm<sup>3</sup>.

30

The system is left to equilibrate for one hour. The temperature of the autoclave is then decreased to 20°C over 65 minutes. The phase in suspension in the supercritical CO<sub>2</sub> thus transforms into a mixture of liquid and gaseous CO<sub>2</sub>, the particles of active principle being in suspension in the liquid CO<sub>2</sub>. By

35

then depressurizing to atmospheric pressure, microparticles of beclomethazone dipropionate covered with DLPG are obtained.

200 mg of nonaggregated particles of beclomethasone dipropionate, with a diameter equal to 5  $\mu$ m, coated with a layer of DLPG, are thus obtained, the active principle/coating agent mass ratio of which is  
5 approximately 90/10. These microparticles have improved nebulization properties.

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## CLAIMS

1. A biocompatible microparticle intended to be inhaled, comprising at least one active principle and at least one layer coating this active principle, which is the external layer of said microparticle, said external layer containing at least one coating agent, characterized in that said microparticle has a mean diameter of between 1  $\mu\text{m}$  and 30  $\mu\text{m}$  and an apparent density of between 0.02  $\text{g/cm}^3$  and 0.8  $\text{g/cm}^3$ , and in that it is possible for it to be obtained according to a method comprising the essential steps which are bringing together a coating agent and an active principle and introducing a supercritical fluid, with stirring in a closed reactor.
2. The microparticle as claimed in claim 1, characterized in that it has a mean diameter of between 1  $\mu\text{m}$  and 15  $\mu\text{m}$ , and even more preferably of between 2  $\mu\text{m}$  and 10  $\mu\text{m}$ , and an apparent density of between 0.05  $\text{g/cm}^3$  and 0.4  $\text{g/cm}^3$ , and in that the active principle/coating agent mass ratio of this particle is between 95/5 and 5/95.
3. The microparticle as claimed in claim 1 or 2, which can be obtained using a method comprising the following steps:
- suspending an active principle in a solution of at least one substantially polar coating agent in an organic solvent, said active principle being insoluble in the organic solvent, said substantially polar coating agent being insoluble in a fluid in the supercritical state, said organic solvent being soluble in a fluid

in the supercritical state,

- bringing the suspension into contact with a fluid in the supercritical state, so as to desolvate in a controlled way the substantially polar coating agent and ensure its coacervation,
- substantially extracting the solvent using a fluid in the supercritical state and discharging the SC fluid/solvent mixture,
- recovering the microparticles.

4. The microparticle as claimed in claim 1 or 2, which can be obtained using a method which consists in suspending an active principle in a supercritical fluid containing at least one coating agent dissolved therein, and then in ensuring the coacervation of the particles by physicochemical modification of the environment.

5. The microparticle as claimed in claim 3, characterized in that the coating agent is chosen from the group made up of

- biodegradable (co)polymers of  $\alpha$ -hydroxy-carboxylic acids, in particular homopolymers and copolymers of lactic acid and glycolic acid, and more particularly PLAs (poly-L-lactide) and PLGAs (poly(lactic-co-glycolic acid)),
- amphiphilic block polymers of the poly(lactic acid)-poly(ethylene oxide) type,
- biocompatible polymers of the poly(ethylene glycol), poly(ethylene oxide) type,
- polyanhydrides, poly(ortho esters), poly- $\epsilon$ -caprolactones and derivatives thereof,
- poly( $\beta$ -hydroxybutyrate), poly(hydroxyvalerate) and poly( $\beta$ -hydroxybutyrate-hydroxyvalerate) copolymers,
- poly(malic acid),

- polyphosphazenes,
  - block copolymers of the poly(ethylene oxide)-poly(propylene oxide) type,
  - poly(amino acids),
  - 5 - polysaccharides,
  - phospholipids such as phosphatidyl glycerols, diphosphatidyl glycerols containing C12 to C18 fatty acid chains (DLPG, DMPG, DPPG, DSPG), phosphatidylcholines, diphosphatidylcholines
  - 10 containing C12 to C18 fatty acid chains (DLPC, DMPC, DPPC, DSPC), diphosphatidylethanolamines containing C12 to C18 fatty acid chains (DLPE, DMPE, DPPE, DSPE), diphosphatidylserine containing C12 to C18 chains (DLPS, DMPS, DPPS, DSPS), and mixtures which contain the
  - 15 phospholipids mentioned,
  - fatty acid esters such as glyceryl stearates, glyceryl laurate, cetyl palmitate, or mixtures which contain these compounds,
  - 20 - mixtures which contain the abovementioned compounds.
6. The microparticle as claimed in claim 4, characterized in that the coating agent is chosen
- 25 from the group made up of
- phospholipids such as phosphatidyl glycerols, diphosphatidyl glycerols containing C12 to C18 fatty acid chains (DLPG, DMPG, DPPG, DSPG), phosphatidylcholines, diphosphatidylcholines
  - 30 containing C12 to C18 fatty acid chains (DLPC, DMPC, DPPC, DSPC), diphosphatidylethanolamines containing C12 to C18 fatty acid chains (DLPE, DMPE, DPPE, DSPE), diphosphatidylserine containing C12 to C18 chains (DLPS, DMPS, DPPS, DSPS), and mixtures which contain the
  - 35 phospholipids mentioned,
  - mono-, di-, triglycerides in which the fatty acid chains range from C4 to C22, and mixtures

containing them,

- mixtures of glycerides and of esters of polyethylene glycol,
- cholesterol,
- 5 - fatty acid esters such as glyceryl stearates, glyceryl laurate or cetyl palmitate,
- biodegradable or bioerodible polymers soluble in a supercritical fluid,
- mixtures which contain the abovementioned
- 10 compounds.

7. The microparticle as claimed in any one of claims 1 to 6, characterized in that the active principle is chosen from the group made up of proteins and peptides, such as insulin, calcitonin, or analogues of the hormone LH-RH, polysaccharides such as heparin, anti-asthmatic agents, such as budesonide, beclometasone dipropionate and its active metabolite beclometasone 17-monopropionate, beta-estradiol hormones, testosterone, broncho-dilators such as albuterol, cytotoxic agents, corticoids, antigens and DNA fragments.

15

20

8. The microparticle as claimed in claim 2, characterized in that the microparticle is an immediate-release microparticle and that the active principle/coating agent mass ratio of this particle is between 95/5 and 80/20.

25

9. A method for preparing microparticles intended to be inhaled, and comprising the following steps:

- suspending an active principle in a solution of at least one substantially polar coating agent in an organic solvent,
- 35 said active principle being insoluble in the organic solvent,
- said substantially polar coating agent being insoluble in a fluid in the supercritical

state,

said organic solvent being soluble in a fluid  
in the supercritical state,

- 5           - bringing the suspension into contact with a  
          fluid in the supercritical state, so as to  
          desolvate in a controlled way the substantially  
          polar coating agent and ensure its  
          coacervation,
  - 10          - substantially extracting the solvent using a  
          fluid in the supercritical state and  
          discharging the SC fluid/solvent mixture,
  - recovering the microparticles.
10.   A method for preparing microparticles intended to  
15   be inhaled, which consists in suspending, with  
     stirring in a closed reactor, an active principle  
     in a supercritical fluid containing at least one  
     coating agent dissolved therein, and then in  
20   ensuring the coacervation of the particles by  
     physicochemical modification of the environment.

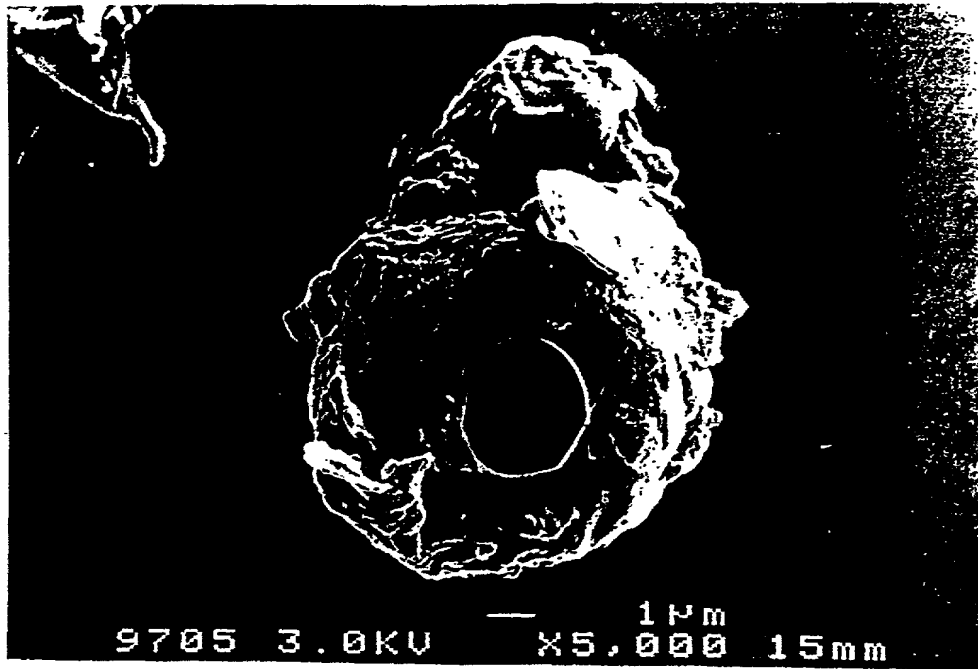


FIGURE 1

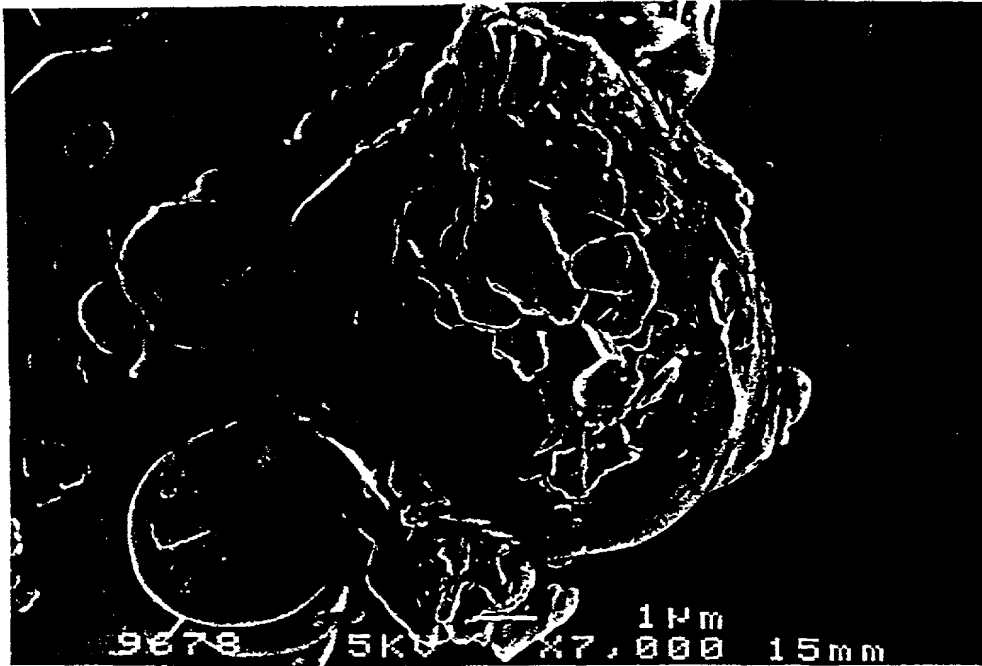


FIGURE 2

## DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first, and sole inventor (if only one name is listed below) or an original, first, and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: **MICROPARTICLES FOR PULMONARY ADMINISTRATION**

the specification of which ☐ is attached and/or ☒ was filed on August 9, 2000 as PCT International Application No. FR/00/02282 and was amended on (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate or § 365(a) of any PCT International application(s) designating at least one country other than the United States, listed below and have also identified below, any foreign application(s) for patent or inventor's certificate, or any PCT International application(s) having a filing date before that of the application(s) of which priority is claimed:

Country	Application Number	Date of Filing	Priority Claimed Under 35 U.S.C. 119	
FRANCE	99 10411	August 11, 1999	<input checked="" type="checkbox"/> YES	<input type="checkbox"/> NO
			<input type="checkbox"/> YES	<input type="checkbox"/> NO

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:

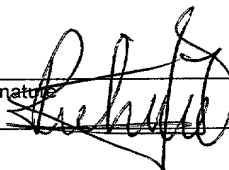
Application Number	Date of Filing

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) or § 365(c) of any PCT International application(s) designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application(s) in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application(s) and the national or PCT International filing date of this application:

Application Number	Date of Filing	Status (Patented, Pending, Abandoned)
PCT/FR00/02282	August 9, 2000	PENDING

I hereby appoint the following attorney and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: **FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER L.L.P.**, Douglas B. Henderson, Reg. No. 20,291; Ford F. Farabow, Jr., Reg. No. 20,630; Arthur S. Garrett, Reg. No. 20,338; Donald R. Dunner, Reg. No. 19,073; Brian G. Brunsvold, Reg. No. 22,593; Tipton D. Jennings, IV, Reg. No. 20,645; Jerry D. Voight, Reg. No. 23,020; Laurence R. Hefter, Reg. No. 20,827; Kenneth E. Payne, Reg. No. 23,098; Herbert H. Mintz, Reg. No. 26,691; C. Larry O'Rourke, Reg. No. 26,014; Albert J. Santorelli, Reg. No. 22,610; Michael C. Elmer, Reg. No. 25,857; Richard H. Smith, Reg. No. 20,609; Stephen L. Peterson, Reg. No. 26,325; John M. Romary, Reg. No. 26,331; Bruce C. Zotter, Reg. No. 27,680; Dennis P. O'Reilly, Reg. No. 27,932; Allen M. Sokal, Reg. No. 26,695; Robert D. Bajefsky, Reg. No. 25,387; Richard L. Stroup, Reg. No. 28,478; David W. Hill, Reg. No. 28,220; Thomas L. Irving, Reg. No. 28,619; Charles E. Lipsey, Reg. No. 28,165; Thomas W. Winland, Reg. No. 27,605; Basil J. Lewis, Reg. No. 28,818; Martin I. Fuchs, Reg. No. 28,508; E. Robert Yoches, Reg. No. 30,120; Barry W. Graham, Reg. No. 29,924; Susan Haberman Griffen, Reg. No. 30,907; Richard B. Racine, Reg. No. 30,415; Thomas H. Jenkins, Reg. No. 30,857; Robert E. Converse, Jr., Reg. No. 27,432; Clair X. Mullen, Jr., Reg. No. 20,348; Christopher P. Foley, Reg. No. 31,354; John C. Paul, Reg. No. 30,413; Roger D. Taylor, Reg. No. 28,992; David M. Kelley, Reg. No. 30,953; Kenneth J. Meyers, Reg. No. 25,146; Carol P. Einaudi, Reg. No. 32,220; Walter Y. Boyd, Jr., Reg. No. 31,738; Steven M. Anzalone, Reg. No. 32,095; Jean B. Fordis, Reg. No. 32,984; Barbara C. McCurdy, Reg. No. 32,120; James K. Hammond, Reg. No. 31,964; Richard V. Burgujian, Reg. No. 31,744; Michael Jakes, Reg. No. 32,824; Dirk D. Thomas, Reg. No. 32,600; Thomas W. Banks, Reg. No. 32,719; Christopher P. Isaac, Reg. No. 32,616; Bryan C. Diner, Reg. No. 32,409; M. Paul Barker, Reg. No. 32,013; Andrew Chanhon Sonu, Reg. No. 33,457; David S. Forman, Reg. No. 33,694; Vincent P. Kovalick, Reg. No. 32,867; James W. Edmondson, Reg. No. 33,871; Michael R. McGurk, Reg. No. 32,045; Joann M. Neth, Reg. No. 36,363; Gerson S. Panitch, Reg. No. 33,751; Cheri M. Taylor, Reg. No. 33,216; Charles E. Van Horn, Reg. No. 40,266; and Linda A. Wadler, Reg. No. 33,218; and  
Please address all correspondence to **FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.** 1300 I Street, N.W. Washington, D.C. 20005, Telephone No. (202) 408-4000.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

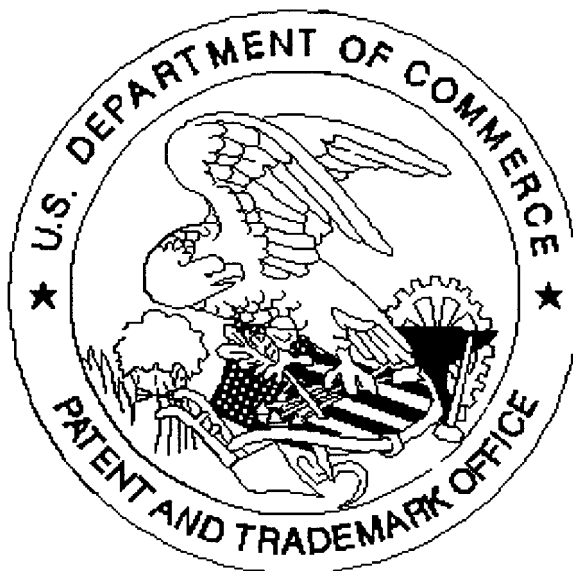
Full Name of First Inventor <b>Joël RICHARD</b>	Inventor's Signature 	Date <b>January 31, 2002</b>
Residence <b>La Modtais, Blou - 49160 Longue / France</b>	<b>FR X</b>	Citizenship <b>France</b>
Post Office Address <b>The same as residence</b>		

2-00	Full Name of Second Inventor <b>Claire DULIEU</b>	Inventor's Signature <i>Claire Dureau</i>	Date <b>January 31, 2002</b>
	Residence <b>33bis rue Racine – 49000 Angers / France</b>		Citizenship France <b>FRX</b>
	Post Office Address The same as residence		
3-00	Full Name of Third Inventor <b>Dominique LE MEURLAY</b>	Inventor's Signature <i>D. Le Meurlay</i>	Date <b>January 31, 2002</b>
	Residence <b>17 avenue du Général Lamoricière – 49100 Angers / France</b>		Citizenship France <b>FRX</b>
	Post Office Address The same as residence		
4-00	Full Name of Fourth Inventor <b>Jean-Pierre BENOIT</b>	Inventor's Signature <i>J. Benoit</i>	Date <b>January 31, 2002</b>
	Residence <b>45 allée des Châtaigniers – 49240 Avrillé / France</b>		Citizenship France <b>FRX</b>
	Post Office Address The same as residence		
	Full Name of Fifth Inventor	Inventor's Signature	Date
	Residence		Citizenship
	Post Office Address		
	Full Name of Sixth Inventor	Inventor's Signature	Date
	Residence		Citizenship
	Post Office Address		
	Full Name of Seventh Inventor	Inventor's Signature	Date
	Residence		Citizenship
	Post Office Address		
	Full Name of Eighth Inventor	Inventor's Signature	Date
	Residence		Citizenship
	Post Office Address		
	Full Name of Ninth Inventor	Inventor's Signature	Date
	Residence		Citizenship
	Post Office Address		
	Full Name of Tenth Inventor	Inventor's Signature	Date
	Residence		Citizenship
	Post Office Address		
	Full Name of Eleventh Inventor	Inventor's Signature	Date
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